

Ticagrelor Versus Clopidogrel in Patients With Acute Coronary Syndromes and Chronic Obstructive Pulmonary Disease: An Analysis From the Platelet Inhibition and Patient Outcomes (PLATO) Trial

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Background—Patients with chronic obstructive pulmonary disease (COPD) experiencing acute coronary syndromes (ACS) are at high risk for clinical events. In the Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor versus clopidogrel reduced the primary endpoint of death from vascular causes, myocardial infarction, or stroke after ACS, but increased the incidence of dyspnea, which may lead clinicians to withhold ticagrelor from COPD patients.

Methods and Results—In 18 624 patients with ACS randomized to treatment with ticagrelor or clopidogrel, history of COPD was recorded in 1085 (5.8%). At 1 year, the primary endpoint occurred in 17.7% of patients with COPD versus 10.4% in those without COPD ($P<0.001$). The 1-year event rate for the primary endpoint in COPD patients treated with ticagrelor versus clopidogrel was 14.8% versus 20.6% (hazard ratio [HR]=0.72; 95% confidence interval [CI]: 0.54 to 0.97), for death from any cause 8.4% versus 12.4% (HR=0.70; 95% CI: 0.47 to 1.04), and for PLATO-defined major bleeding rates at 1 year 14.6% versus 16.6% (HR=0.85; 95% CI: 0.61 to 1.17). Dyspnea occurred more frequently with ticagrelor (26.1% vs. 16.3%; HR=1.71; 95% CI: 1.28 to 2.30). There was no differential increase in the relative risk of dyspnea compared to non-COPD patients (HR=1.85). No COPD status-by-treatment interactions were found, showing consistency with the main trial results.

Conclusions—In this post-hoc analysis, COPD patients experienced high rates of ischemic events. Ticagrelor versus clopidogrel reduced and substantially decreased the absolute risk of ischemic events (5.8%) in COPD patients, without increasing overall major bleeding events. The benefit-risk profile supports the use of ticagrelor in patients with ACS and concomitant COPD.

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Key Words: cardiovascular diseases • lung • myocardial infarction

Patients with chronic obstructive pulmonary disease (COPD) are at high risk of experiencing acute coronary syndromes (ACS).¹ This high risk is partly attributed to shared common risk factors, such as higher age, smoking,²

and systemic inflammation.³ In addition, reduced pulmonary function, independent of smoking, has been associated with increased risk of ACS, arrhythmias, and cardiovascular death.^{4–7} Patients with COPD experiencing ACS have

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Accompanying Tables S1 and S2 are available at <http://jaha.ahajournals.org/content/4/10/e002490/suppl/DC1>

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subsequent increased risk of recurrent ischemic events and increased all-cause mortality compared to those without COPD.^{8–11} This is, to a certain extent, explained by comorbidities,¹¹ but it has been shown that patients with COPD are less likely to receive reperfusion therapy and guideline-recommended secondary prevention therapies, which could further worsen long-term outcomes.^{8,9,11,12}

The PLATO study showed superior efficacy of the non-thienopyridine platelet P2Y₁₂-receptor inhibitor, ticagrelor, as compared to clopidogrel in preventing death from vascular causes, myocardial infarction (MI), or stroke in patients with ACS, without an increase in overall major bleeding events.¹³ However, patients randomized to ticagrelor had increased incidence of dyspnea, a known adverse effect commonly characterized as mild to moderate and often transient without being associated with either differences in efficacy or safety outcomes¹⁴ or an adverse effect on pulmonary function.¹⁵ Previous substudies from PLATO have shown ticagrelor to be superior to clopidogrel in different high-risk patient populations, including patients with diabetes¹⁶ or impaired renal function,¹⁷ and in the elderly.¹⁸

Despite ACS patients with concomitant COPD being at higher risk thus warranting efficacious therapies, clinicians may be reluctant to prescribe ticagrelor to these patients owing to the increased incidence of dyspnea. At the time the PLATO trial was published, an accompanying editorial discouraged the use of ticagrelor in patients with COPD.¹⁹ Furthermore, the European Medicines Agency assessment report indicates caution when prescribing ticagrelor to patients with history of COPD, owing to a potentially increased absolute risk of dyspnea.²⁰ Thus, the aim of the present study was to study the efficacy and safety profile of ticagrelor versus clopidogrel in ACS patients with COPD.

Methods

The PLATO trial (<http://www.clinicaltrials.gov> identifier: NCT00391872) enrolled 18 624 patients between October 2006 and July 2008. Details about the study design, patients, outcome definitions, and results have been published.^{13,21} In each country, the study was approved by national regulatory authorities and by local ethics committees or institutional review boards, according to local regulations. All patients provided written consent to participate in the study. Patients were eligible for enrollment if they were hospitalized for ACS, with or without ST-segment elevation, and with symptom onset during the previous 24 hours. Major exclusion criteria were contraindication to clopidogrel, fibrinolytic therapy within 24 hours before randomization, a need for oral anticoagulation therapy, an increased risk of bradycardia, and simultaneous therapy with a strong cytochrome P450 3A

inhibitor or inducer. Patients were randomized to ticagrelor or clopidogrel in a double-blind, double-dummy fashion. All patients received acetylsalicylic acid unless intolerant. The median treatment duration was 9.1 months.

The primary efficacy endpoint was time to first occurrence of any event from the composite endpoint consisting of death from vascular causes, MI, or stroke. Secondary efficacy endpoints were individual events of MI, stroke, death from vascular causes, and death from any cause. The primary safety endpoint was time to first occurrence of major bleeding, defined by the study criteria. In addition, bleeding events defined according to the TIMI criteria, and life-threatening or fatal bleeding (defined by the study criteria) were also assessed. Other adverse events, including dyspnea, were recorded in the electronic case report form. Each on-site investigator assessed COPD status at the time of randomization and reported in the case report form whether the patient had “current COPD” or “no COPD.”

Statistical Analyses

Baseline patient characteristics were compared by COPD status. Continuous variables are presented as medians (25th to 75th percentile) and differences were compared using the Wilcoxon rank-sum test. Categorical variables are presented as counts (percentages) and differences were compared using the Pearson chi-square test when the cell frequencies were sufficient; otherwise, an exact test was used. For patients with and without COPD, Kaplan–Meier event rates 12 months after randomization were calculated separately for ticagrelor- and clopidogrel-treated groups, for each efficacy and safety endpoint. Cox proportional hazards regression was used to characterize the randomized treatment effect in patients with and without COPD. For each endpoint, the hazard ratio (HR; 95% confidence interval [CI]) for the COPD cohort and non-COPD cohort and treatment-by-COPD interaction *P* value are reported. Cox proportional hazard regression was also used to characterize the univariate, age-adjusted, and multivariate HRs with 95% CI for the primary efficacy endpoint in patients with COPD versus patients without COPD. Adjustment covariates include: previous MI, previous nonhemorrhagic stroke, heart rate, Killip class at entry, age, white blood cells, peripheral artery disease, previous coronary artery bypass grafting (CABG), time from symptoms to randomization, diabetes, hemoglobin, region, changes in electrocardiogram at entry, final diagnosis of index event, previous transient ischemic attack, randomized treatment, and creatinine. Continuous variables were assessed for linearity on the log-hazard scale, and, when appropriate, linear splines were used to account for nonlinear relationships with the primary efficacy endpoint.

Table 1. Baseline Characteristic According to COPD Status

Characteristic	COPD (N=1085)	No COPD (N=17 528)	P Value
Demographics			
Age, yr	67 (59 to 73)	62 (54 to 70)	<0.001
Age ≥75 years	236/1085 (21.8)	2640/17 528 (15.1)	<0.001
Female gender	325/1085 (30.0)	4959/17 528 (28.3)	0.239
Race			0.002
Caucasian	1010/1085 (93.1)	16 057/17 528 (91.6)	
Black	19/1085 (1.8)	210/17 528 (1.2)	
Oriental	39/1085 (3.6)	1057/17 528 (6.0)	
Other	17/1085 (1.6)	204/17 528 (1.2)	
BMI, kg/m ²	27.7 (24.2 to 31.1)	27.4 (24.7 to 30.4)	0.644
Waist circumference, cm	100 (90 to 110)	98 (90 to 106)	<0.001
Smoking status			<0.001
Nonsmoker	204/1085 (18.8)	7052/17 525 (40.2)	
Ex-smoker	390/1085 (35.9)	4286/17 525 (24.5)	
Habitual smoker	491/1085 (45.3)	6187/17 525 (35.3)	
Medical history			
Hypertension	783/1085 (72.2)	11 400/17 528 (65.0)	<0.001
Dyslipidemia	585/1085 (53.9)	8104/17 527 (46.2)	<0.001
Diabetes mellitus	292/1085 (26.9)	4370/17 528 (24.9)	0.144
Angina pectoris	632/1085 (58.2)	7726/17 528 (44.1)	<0.001
Myocardial infarction	322/1085 (29.7)	3502/17 528 (20.0)	<0.001
Congestive heart failure	152/1085 (14.0)	898/17 528 (5.1)	<0.001
Coronary artery disease	441/1085 (40.6)	4685/17 528 (26.7)	<0.001
PCI	225/1085 (20.7)	2267/17 527 (12.9)	<0.001
CABG	132/1085 (12.2)	974/17 528 (5.6)	<0.001
Transient ischemic attack	46/1085 (4.2)	453/17 528 (2.6)	0.001
Nonhemorrhagic stroke	47/1084 (4.3)	675/17 528 (3.9)	0.422
Peripheral artery disease	153/1085 (14.1)	991/17 528 (5.7)	<0.001
Pacemaker	23/1085 (2.1)	133/17 528 (0.8)	<0.001
Peptic ulcer disease	122/1085 (11.2)	1151/17 528 (6.6)	<0.001
Gastrointestinal bleeding	44/1085 (4.1)	221/17 528 (1.3)	<0.001
Asthma	118/1085 (10.9)	414/17 528 (2.4)	<0.001
Chronic renal disease	93/1085 (8.6)	692/17 528 (3.9)	<0.001
Biochemistry			
Creatinine clearance [CG], mL/min	73.3 (56.4 to 91.9)	80.7 (63.4 to 99.3)	<0.001
Glucose, mmol/L	6.7 (5.6 to 8.5)	6.9 (5.7 to 8.8)	0.023
HbA1c, %	6.1 (5.7 to 6.7)	6.0 (5.6 to 6.6)	0.020
Hemoglobin, g/L	138 (126 to 148)	140 (129 to 149)	0.002
Total cholesterol, mmol/L	4.8 (4.1 to 5.8)	5.1 (4.4 to 6.0)	<0.001
LDL cholesterol, mmol/L	2.9 (2.2 to 3.6)	3.1 (2.4 to 3.9)	<0.001
HDL cholesterol, mmol/L	1.2 (1.0 to 1.5)	1.2 (1.0 to 1.4)	0.377
First central Tnl positive	883/1085 (81.4)	14 205/17 528 (81.0)	0.889

Continued

Table 1. Continued

Characteristic	COPD (N=1085)	No COPD (N=17 528)	P Value
Medications at randomization			
Aspirin	997/1085 (91.9)	16 428/17 511 (93.8)	0.011
Unfractionated heparin	536/1085 (49.4)	8922/17 511 (51.0)	0.322
Low molecular weight heparin	460/1085 (42.4)	6855/17 511 (39.1)	0.033
GP IIb/IIIa inhibitors	234/1085 (21.6)	4345/17 511 (24.8)	0.016
Beta blockers	673/1085 (62.0)	12 324/17 511 (70.4)	<0.001
ACE inhibitors	628/1085 (57.9)	9893/17 511 (56.5)	0.372
Angiotensin II receptor blockers	126/1085 (11.6)	1519/17 511 (8.7)	<0.001
Statins	839/1085 (77.3)	13 864/17 511 (79.2)	0.147
Calcium channel blockers	181/1085 (16.7)	2527/17 511 (14.4)	0.041
Diuretics	416/1085 (38.3)	3906/17 511 (22.3)	<0.001
Proton pump inhibitors	427/1085 (39.4)	5946/17 511 (34.0)	<0.001
Nitrates	794/1085 (73.2)	12 235/17 511 (69.9)	0.021
Intended treatment approach			0.004
Invasive	740/1085 (68.2)	12 658/17 528 (72.2)	
Medically managed	345/1085 (31.8)	4870/17 528 (27.8)	
Final diagnosis			<0.001
NSTEMI/UA	736/1085 (67.8)	10 333/17 528 (59.0)	
STEMI	349/1085 (32.2)	7195/17 528 (41.0)	

ACE indicates angiotensin-converting enzyme; BMI, body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; GP IIb/IIIa, glycoprotein IIb/IIIa; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TnI, troponin I; UA, unstable angina.

All analyses were performed according to the intention-to-treat definition with SAS software (version 9.2; SAS Institute Inc., Cary, NC). A 2-sided *P* value of 0.05 was considered statistically significant for overall treatment differences.

Results

Patient Characteristics

Of 18 624 patients randomized in the PLATO study, 1085 (5.8%) were reported by the investigators as having COPD. These patients were older and more often current or ex-smokers (Table 1). They more frequently had multiple cardiovascular risk factors and comorbidities, including a history of angina pectoris, MI, congestive heart failure, and coronary artery disease. In addition, COPD patients had lower median creatinine clearance, were less often treated with beta-blockers, and more often treated with diuretics. In regard to treatment approach, patients with COPD were less frequently invasively investigated. Furthermore, fewer COPD patients were diagnosed with ST-segment elevation myocardial infarction (STEMI).

Baseline characteristics, medications, and treatment approach were well matched between the randomized treatment groups (Table S1).

Ischemic and Bleeding Outcomes in Relation to COPD Status and Randomized Treatment

Rates of both ischemic and bleeding events were higher in patients with COPD compared to those without COPD (Figure 1), and crude all-cause mortality was doubled (10.4% vs. 4.9%; HR=2.09; 95% CI: 1.70 to 2.57). The univariate, age-adjusted, and multivariate HRs for the primary composite endpoint for COPD patients versus non-COPD patients were 1.75 (95% CI: 1.50 to 2.04), 1.53 (95% CI: 1.31 to 1.79), and 1.31 (95% CI: 1.09 to 1.57), respectively.

Ticagrelor significantly reduced the primary composite endpoint of death from vascular causes, MI, or stroke, both in patients with or without COPD (Figures 1 and 2). The relative reduction in the rate of the primary endpoint with ticagrelor was similar between COPD and non-COPD patients and consistent with the main trial findings, but the absolute reduction was greater in patients with COPD (5.8% vs. 1.5%).

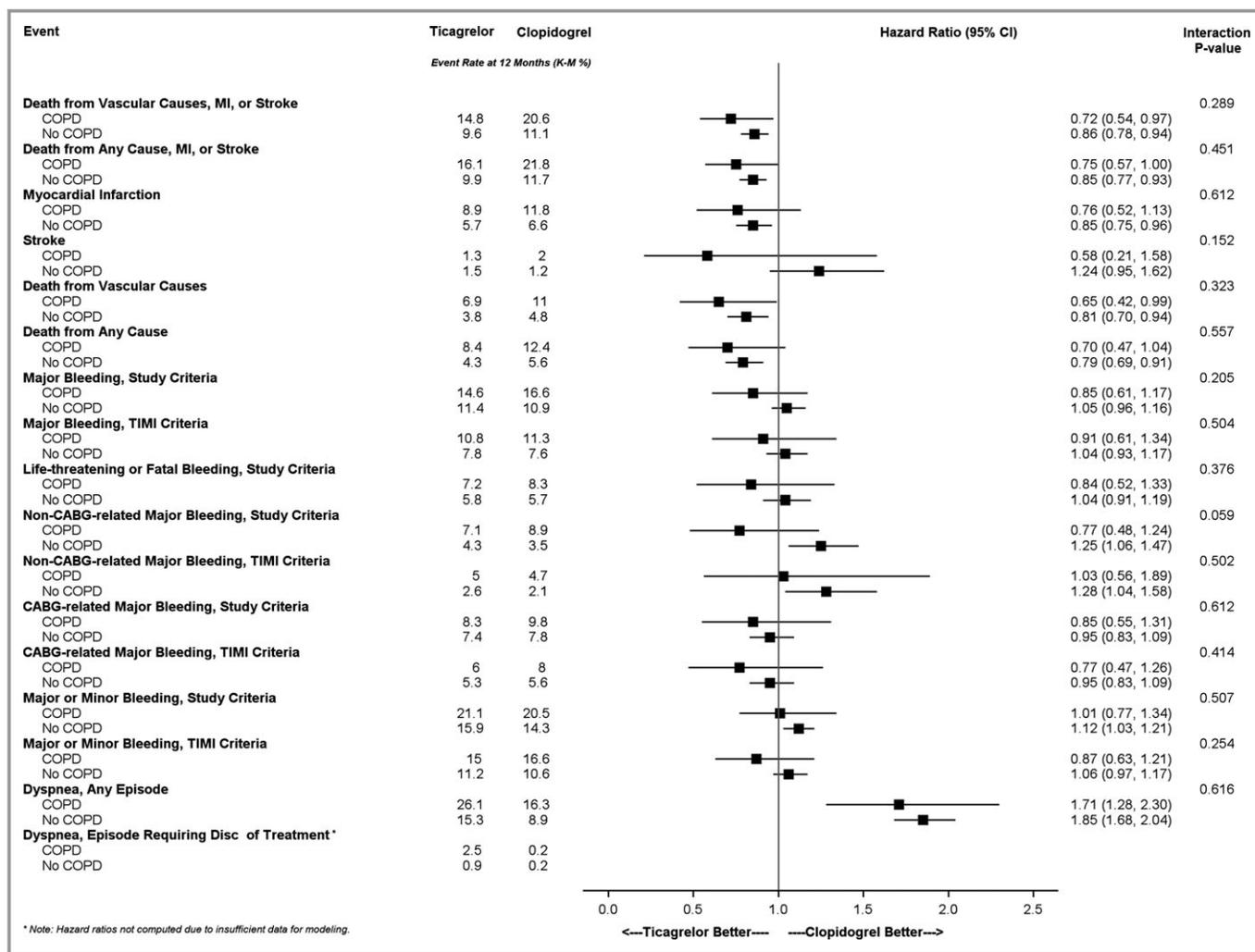


Figure 1. The percentages are Kaplan–Meier (K-M) estimates of the rate of the endpoint at 12 months. CABG indicates coronary artery bypass graft; CI, confidence interval; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; TIMI, thrombolysis in myocardial infarction study group.

No COPD status-by-treatment interactions were found in the efficacy endpoint analyses. In line with the main trial, ticagrelor was associated with a reduction in death from any cause in patients with or without COPD (interaction $P=0.557$).

For COPD and non-COPD patients, no significant difference in the rates of overall major bleeding, regardless of using PLATO (Figure 3) or thrombolysis in myocardial infarction study group (TIMI) criteria, was observed between ticagrelor- and clopidogrel-treated patients (Figure 1). In accord with the main trial, ticagrelor was associated with increased PLATO-defined non-CABG-related major bleeding in non-COPD patients, but in COPD patients these rates were similar, although the interaction analysis was not significant ($P=0.059$). No interaction tests were significant irrespective of bleeding type and definition.

Dyspnea-Related Outcomes, Discontinuation of Study Drug, and Adverse Events

Ticagrelor significantly increased the incidence of dyspnea, both in patients with and without COPD (Figure 1). Although absolute dyspnea event rates were higher in COPD patients, ticagrelor-associated relative risks were similar and no COPD status-by-treatment interaction was found ($P=0.616$). Dyspnea-related discontinuation of study drug was more common with ticagrelor, irrespective of COPD status. COPD patients treated with ticagrelor showed numerically more dyspnea-related events leading to discontinuation of study drug compared to non-COPD patients (2.5% vs. 0.9%), although the numbers of discontinuations were very small. Overall premature discontinuation of study drug was more common in COPD patients treated with ticagrelor (Table 2).

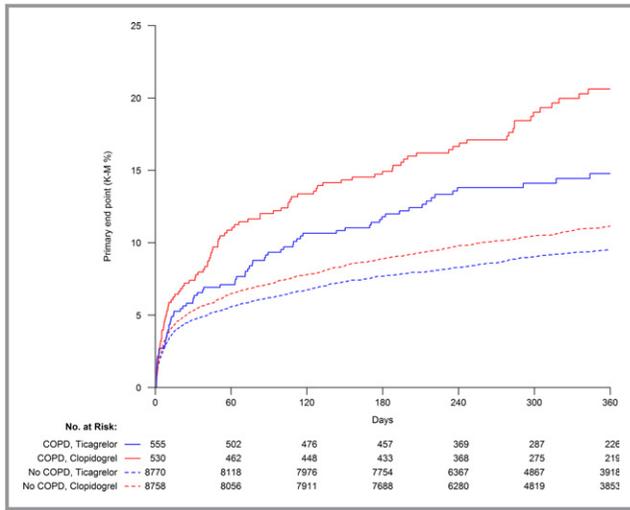


Figure 2. Cumulative Kaplan–Meier estimates of the time to first adjudicated occurrence of the primary efficacy endpoint (a composite of death from vascular causes, myocardial infarction, or stroke). Chronic obstructive pulmonary disease (COPD) patients randomized to ticagrelor or clopidogrel are represented by solid blue and red lines, respectively, and non-COPD patients randomized to ticagrelor or clopidogrel are represented by dashed blue and red lines, respectively. K-M indicates Kaplan–Meier.

Adherence to study drug, defined as the use of more than 80% of the study medication during each interval between visits, was slightly higher in COPD patients treated with ticagrelor, whereas the exposure, meaning total days on treatment, was slightly lower. There were more adverse

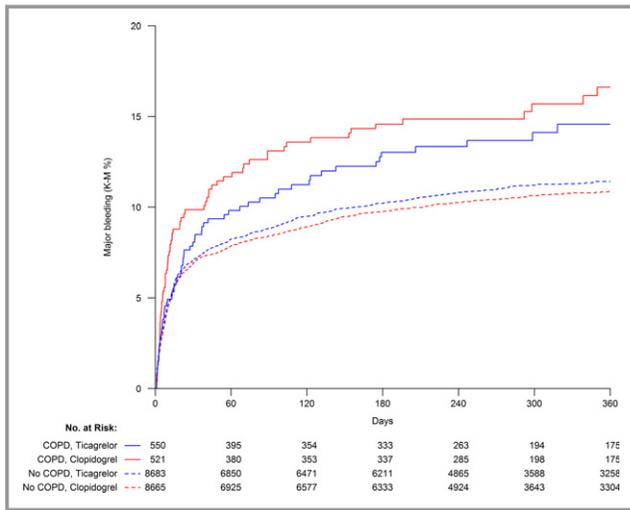


Figure 3. Cumulative Kaplan–Meier estimates of the time to first PLATO-defined major bleeding event. COPD patients randomized to ticagrelor or clopidogrel are represented by solid blue and red lines, respectively, and non-COPD patients randomized to ticagrelor or clopidogrel are represented by dashed blue and red lines, respectively. COPD indicates chronic obstructive pulmonary disease; K-M, Kaplan–Meier; PLATO, Platelet Inhibition and Patient Outcomes.

Table 2. Randomized Treatment Use and Dyspnea-Related AEs

No. of COPD Patients, No. (%)	Ticagrelor (n=555)	Clopidogrel (n=530)
Discontinuation and adherence		
Premature discontinuation of study drug	184 (33.2)	140 (26.4)
Adherence* to study drug	436 (78.6)	395 (74.5)
Exposure to study drug, median (IQR)	266 (65 to 364)	278 (99 to 364)
AE summary		
Dyspnea as the predominant symptom	111 (20.0)	64 (12.1)
SAE	10 (1.8)	5 (0.9)
AE is serious owing to[†]—No./SAE (%)		
Death	0/10 (0.0)	0/5 (0.0)
Life threatening	3/10 (30.0)	0/5 (0.0)
In-patient hospitalization or prolongation of hospitalization	10/10 (100.0)	5/5 (100.0)
Persistent or significant disability/incapacity	2/10 (20.0)	1/5 (20.0)
A congenital abnormality/birth defect	0/10 (0.0)	0/5 (0.0)
Important medical event	5/10 (50.0)	1/5 (20.0)

AE indicates adverse event; COPD chronic obstructive pulmonary disease; IQR, interquartile range; SAE, serious AE.

*Adherence to the study drug was defined as the use of more than 80% of the study medication during each interval between visits, as assessed by the site investigator.

[†]According to the SAE Report form, a patient can have multiple criteria selected for classifying the AE as serious.

events (AEs) related to dyspnea in patients with COPD treated with ticagrelor (Table 2). The numbers of serious AEs (SAEs) were small. The suspected etiologies of dyspnea events are shown in Table S2.

Subgroup Analyses

Efficacy and safety outcomes in subgroups defined by initial treatment approach (invasive investigation vs. medically managed) were consistent with the main findings (data not shown). Likewise, an additional analysis with nonsmokers excluded was also consistent with the main findings (data not shown).

Discussion

In line with other published studies,^{8–11} the PLATO trial highlights patients with COPD as a high-risk population when experiencing ACS, shown by both increased risk of recurrent ischemic and bleeding events as well as by doubled crude

all-cause mortality after an ACS. In the present study, patients with COPD were older with a particularly high-risk profile, including higher prevalence of congestive heart failure, coronary artery disease, and chronic renal disease findings similar to previous observational data.^{11,22} In regard to treatment approach, COPD patients were slightly less often planned for invasive investigation, but guideline-recommended therapies were still prescribed to a high extent (except beta-blockers), a finding in contrast with the general undertreatment observed in many observational studies.^{8,11,12,23}

The most important finding in the present study is that ticagrelor, compared to clopidogrel, significantly reduced the primary efficacy endpoint consisting of death from vascular causes, MI, and stroke regardless of COPD status, without increasing the rate of overall major bleeding. In the COPD subset, the absolute risk reduction by ticagrelor versus clopidogrel was 4 times greater, as compared to those without COPD. The findings in this study and other high-risk subgroup analyses from PLATO suggest that patients at greater risk have increased absolute benefit of ticagrelor.^{16,17,24}

In terms of bleeding, the results from the present study align with the main trial results, with similar overall major bleeding rates between ticagrelor- and clopidogrel-treated groups. In the main trial, PLATO-defined non-CABG-related major bleeding was increased in patients treated with ticagrelor. However, in the present study, this increase was found in the non-COPD-cohort, but not in the COPD cohort, though the interaction analysis did not reach statistical significance ($P=0.059$).

Although there was no relative increase in ticagrelor-related dyspnea in the COPD cohort, there was a higher absolute risk of dyspnea in these patients. Even though more than 1 quarter of the ticagrelor-treated COPD patients experienced dyspnea, only 2.5% of these patients discontinued ticagrelor because of dyspnea, compared to 0.9% among ticagrelor-treated patients without COPD. Furthermore, the number of SAEs related to dyspnea was few and none were fatal. Most important, the overall ischemic event rate was much lower in the ticagrelor-treated COPD subset, despite the high incidence of dyspnea, in accord with previous studies of ticagrelor-related dyspnea showing that it is often transient and usually mild to moderate in severity without any adverse effect on either lung or heart function.^{14,15,25}

Limitations

This study was a post-hoc analysis not prespecified in the original trial design. The COPD cohort of 1085 patients was not powered to show a difference in the primary outcome between the randomized groups. The randomization in PLATO was not stratified for COPD status; therefore, some imbalance between the groups may exist among the subset of patients with COPD.

Still, the COPD groups stratified by treatment were well balanced regarding baseline characteristics. Furthermore, because COPD status was assessed by the investigators and not based on pulmonary function tests, the COPD cohort may represent a more clinically evident and severe COPD phenotype. However, the assessments performed by the PLATO investigators probably reflect the routine clinical setting.

Conclusions

Patients with ACS and concomitant COPD are a high-risk population with a worse ischemic outcome as well as increased bleeding rates. Ticagrelor significantly reduced the risk of ischemic events with an absolute reduction in COPD patients that was nearly 4 times as great as in non-COPD patients, without an increase in overall major bleeding. There was no differential increase in the relative risk of dyspnea compared to non-COPD patients, but the increase in absolute risk was greater in COPD patients. Although a post-hoc analysis, the benefit-risk profile supports the use of ticagrelor in patients with ACS and COPD. In consideration of the accumulated evidence that patients with COPD constitute a high-risk population with a poor prognosis, who may also be undertreated with guideline-recommended secondary prevention, ticagrelor presents an opportunity to improve outcomes in patients with ACS and COPD.

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